Remarks

Applicants acknowledge with appreciation that the Examiner has withdrawn the rejections under 35 U.S.C. § 103(a) over El-Kafrawy *et al.*

It is noted that the Examiner has inadvertently incorrectly stated on page 2, line 3 of the Office Action that claims 8-12 and 14-20 are pending.

Applicants respectfully request that this Amendment under 37 C.F.R. § 1.116 be entered by the Examiner, placing claims 1-12, 14, 15, 17-26, 28, 29, 31-39, 41-48, 50, 51, 59-61, 63-66, and 68-72 in condition for allowance or materially reducing the number of issues for appeal. Applicants submit that the proposed amendments of claims 1, 2, 17, 31, 39, 41, 50, 51, 59, 60, 63, and 68-71, and proposed new claim 72 do not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner, since all the elements and their relationships claimed were earlier claimed.

Upon entry of the foregoing amendment, claims 1-12, 14, 15, 17-26, 28, 29, 31-39, 41-48, 50, 51, 59-61, 63-66, and 68-72 are pending in the application, with claims 1, 2, 39, 50, 59, 63, 68, 69, and 72 being the independent claims. The specification and claims 1, 2, 17, 31, 39, 41, 50, 51, 59, 60, 63, and 68-71 are sought to be amended. New claim 72 is sought to be added. Claims 62 and 67 are sought to be canceled with prejudice to or disclaimer of the subject matter therein, as being redundant in view of the amendments made to claims 1 and 50. These changes are believed to introduce no new matter, and their entry is respectfully requested. Applicants assert the right to file one or more continuing applications for the subject-matter canceled. Support for the amendments and new claim 72 can be found in the original specification and claims as filed.

The specification has been amended by inserting a sheet of FIGS. 1A-1D at the end of the application that correspond to the Fig. 1 on page 31 of the original specification. The symbols A, B, C, and D in the drawing have been amended to read

D

FIG. 1A, FIG. 1B, FIG. 1C, and FIG. 1D, respectively. No new matter has been added by this amendment.

The specification has also been amended by inserting a new paragraph entitled "BRIEF DESCRIPTION OF THE DRAWINGS" after paragraph [0021]. This new paragraph includes the first sentence of paragraph [0122] and the figure text below the Fig. 1. The symbols A, B, C, and D of the figure text have been amended to read FIG. 1A, FIG. 1B, FIG. 1C, and FIG. 1D, respectively. No new matter has been added by this amendment.

The specification has been also amended by deleting Fig. 1 and the figure text from paragraph [0122] at page 31. Further, paragraph [0122] has been amended by adding --**A**, **B**, **C**, and **D**-- after "protocols" at line 1 of the paragraph and replacing "(Fig. 1)" with --(FIGS. 1A-1D)--. Paragraph [0122] has also been amended by adding --(FIG. 1A)-- after "protocol **A**", --(FIG. 1C)-- after "protocol **C**", --(FIG. 1B)-- after "Protocol **B**", and --(FIG. 1D)-- after the first "protocol **D**". No new matter has been added by these amendments.

In order to advance the prosecution of the pending claims, claims 1, 2, 17, 31, 41, 50, 63, and 68-71 have been amended by deleting the term "prodrug", and claims 1, 2, 50, 63, and 68-71 have been amended by deleting the term "carbonylamido" from the definitions for the substituents R_3, R_4, R_5, and R_6. Applicants submit that no new matter has been introduced by these amendments since deletion of individual members of Markush expression does not constitute new matter. See, *In re Johnson and Farnham*, 194 U.S.P.Q. 187 (CCPA 1977).

Claims 1, 50, 63, 68, and 69 have been amended by replacing the term "aminocarbonyl" with -- —$C(O)NH_2$ -- in the proviso "provided that when Y is R_7, R_1 is aminocarbonyl" to make the claims more clear. Support for this amendment is found at page 19, paragraph [0090], of the specification as originally filed.

Claims 39 and 59 have been amended to be independent claims. In addition, claim 51 has been amended to be dependent on claims 1, 2, 63, 69, 70, or 71, instead of

claims 1, 2, 63, or 69. Claim 60 has been amended by replacing the term "A compound" with --The compound--. New claim 72, directed to a pharmaceutical composition, is supported by claims 50 and 51 as originally filed.

No new matter has been introduced into the captioned application.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 1-12, 14-15, 17-26, 28-29, 31-39, 41-48, 50-51 and 59-71 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner states that "[a]ny claim not specifically rejected is rejected as being dependent on a rejected claim for reasons of record." Applicants respectfully traverse this rejection.

I. "Prodrug"

The Examiner states that "[i]n claim [*sic*]1-2, 17, 31 and 50 recitation of the term "prodrug" is deemed as indefinite." Applicants respectfully disagree for the reasons of record. However, in order to expedite the prosecution of the pending claims, Applicants have deleted the term "prodrug" in the rejected claims 1-2, 17, 31, and 50, in claims 41, 70, and 71 that are dependent on the rejected claim, and in claims 63, 68, and 69. Thus, the Examiner's rejection has been rendered moot.

II. "Aminocarbonyl"

The Examiner has repeated the following:

> Claims also recite "aminocarbonyl" group and "carboxamido" group that render these claims indefinite as

> it is not clear what is the difference. It implies more than what is positively recited in either of the group.

(Office Action, page 4, lines 1-3).

Further, according to the Examiner,

> the point here is "aminocarbonyl" is a generic term as recited in the claims and that there are two possible point [*sic*] of attachment either through nitrogen of the amine or carbonyl group. That is fine.

(Office Action, page 4, lines 7-9).

Applicants disagree. As stated earlier, according to the specification as originally filed, an aminocarbonyl group is "-$C(O)NH_2$". See paragraph [0090] at page 19. See also claim 41 as originally filed showing that R_1 is -$C(O)NH_2$, i.e., aminocarbonyl, when Y is R_7 as required in claim 1. Applicants submit that there is no basis in the application as filed for any definition for "aminocarbonyl" other than "-$C(O)NH_2$" as defined at paragraph [0090]. There is only one point of attachment in the -$C(O)NH_2$ group and that is the carbonyl carbon. Therefore, in the context of the present invention, aminocarbonyl is not a generic term.

The Examiner continues as follows:

> But the definition of variable group R_1 permits COR_8 where R_8 [*sic*] amino [*sic*] alkyl amino etc. Thus it is not clear what aminocarbonyl group to be used as limitation. Again the definition of various R groups includes amide, carbonyl amide, aminocarbonyl, acylamino. Taken together there is ambiguity and it would not be possible for one trained to know what is included or excluded. Hence this rejection is still deemed as proper and is maintained.

(Office Action, page 4, lines 10-16).

Applicants disagree. As discussed above, it is clear that "aminocarbonyl" has only one meaning which is "-$C(O)NH_2$" and, thus, there is only one aminocarbonyl group, -$C(O)NH_2$, to be used a limitation.

Applicants have amended claims 1, 50, 63, 68, and 69 by replacing the term "aminocarbonyl" with -- —$C(O)NH_2$ -- in the proviso "provided that when Y is R_7, R_1 is

aminocarbonyl" to make claims 1, 50, 63, 68, and 69 more clear. Support for this amendment is found at page 19, paragraph [0090], of the specification as originally filed.

Further, Applicants respectfully submit that it would be clear to one skilled in the art that when R_8 in COR_8 is, e.g., an amino or an alkylamino group, then an aminocarbonyl group (i.e., $-C(O)NH_2$), or an alkylaminocarbonyl group (i.e., -C(O)NH-alkyl), respectively, is formed as defined in paragraphs [0090] and [0091], respectively, of the application as originally filed.

Further, it would be clear to one skilled in the art that an "amide" group is "-NHC(O)-", as defined at paragraph [0097] of the application as filed, wherein the carbonyl carbon is bonded directly to the parent moiety.

The term "acylamino" has a definition at paragraph [0082] of the specification as originally filed. Accordingly, an "acylamino" group is a generic term for a group that has an acyl group attached to an amino nitrogen. The nitrogen atom is bonded directly to the parent moiety.

Regarding the term "carbonyl amide" recited by the Examiner, Applicants wish to point out that the term "carbonylamido" instead of "carbonyl amide" is recited in the claims. However, in order to expedite the prosecution of the pending claims, Applicants have deleted the term "carbonylamido" throughout the claims. Accordingly, claims 1, 2, 50, 63, and 68-71 have been amended by deleting the term "carbonylamido".

In view of the above, it is respectfully submitted that there is no ambiguity and, therefore, one skilled in the art would know what is included in or excluded from the claims.

Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, of claims 1-12, 14-15, 17-26, 28-29, 31-39, 41-48, 50-51, and 59-71 are respectfully requested.

Rejection under 35 U.S.C. § 102(b)

The Examiner has rejected claims 1, 50-51, and 61-69 under 35 U.S.C. § 102(b) as allegedly being anticipated by Tsutomu *et al.* (GB 2,095,240). The rejection is the same as in the previous Office Action except that the newly added claim 69 is included in this rejection. Applicants respectfully traverse this rejection.

The Examiner repeats the previous rejection as follows:

> Tsutomu et al. teaches several pyrimidine compounds, which include those claimed in the instant claims generically, for use as anti-allergic agents. See page 1, formula I and note the definition of R_1 includes (un)substituted aryl. Note the process for making it. Particularly note, Tsutomu et al teaches the intermediate compound of formula II which is also embraced in the instant claims. See page 2 for details of the process and pages 3-13 for compounds made.

(Office Action, page 5, lines 3-8).

Applicants traversed the rejection in the previous Amendment and Reply giving reasons as to why Tsutomu *et al.*, and specifically, formula (I) on page 1 and formulae (IIa), (IIb), (IIc), and (IId) on page 2 do not describe any compound embraced by Applicants' claims and, thus, do not anticipate any of the pending claims. Since the rejection is maintained based on the previous reasons of record and Applicants are unable to find any compound in Tsutomu *et al.* that would fall into the scope of the pending claims, Applicants respectfully request that the Examiner specify in detail which specific compounds described in Tsutomu *et al.* anticipate the pending claims.

Further, the Examiner states that

> applicants seem to rely on the abstract but still traverse the rejection as not teaching even pharmaceutical composition. Note the Title of the abstract includes pharmaceutical composition.

(Office Action, page 5, lines 12-14).

Applicants stated the following on page 17, lines 9-12, of the previous Amendment and Reply: "For the same reasons, Tsutomu *et al.* do not disclose a

pharmaceutical composition as claimed in claim 50 or claim 68." Both claims 50 and 68 of the present application recite compounds that are not taught or suggested by Tsutomu *et al.* Even though the title of the abstract includes the phrase "pharmaceutical composition" as stated by the Examiner, Tsutomu *et al.* do not teach each and every element of claim 50 or 68, *i.e.*, the chemical compounds recited in both of those claims. It follows that Tsutomu *et al.* do not teach the pharmaceutical compositions of claims 50 and 68. Therefore, claims 50 and 68 are not anticipated by Tsutomu *et al.* See M.P.E.P. § 2131.

Further, the Examiner states that

> applicants argue that optionally substituted phenyl attached to the pyrimidine ring is not taught by the reference. See example 11 on page 10, example 15 On [*sic*] page 11. Not all examples 1-20 include a carboxylic acid group for instant R_1 as well as "aminocarbonyl" group which is in the case COR_8, R_8 being a heterocyclic group.

(Office Action, page 5, lines 15-19).

The substituent R^1 of Tsutomu *et al.* corresponds to the optionally substituted Y-X-phenyl- group in the compounds of Formula I of the present invention. Y is defined as (1) an optionally substituted phenyl group or (2) R_7. R_7 is an optionally substituted alkyl. The claims of the present invention require that when Y is R_7, R_1 has to be $-C(O)NH_2$.

Tsutomu *et al.* describe at page 1, lines 15-24, that "R^1 is . . . aryl which may bear one or more substituent(s) selected from the group halogen, hydroxy, nitro, amino, di(lower)alkylamino, lower alkoxy and ar(lower)alkoxy." Thus, assuming "aryl" can be a phenyl group (see page 1, line 24 of Tsutomu *et al.*), R^1 can be any of the following groups: halogen-phenyl-; HO-phenyl-; O_2N-phenyl-; H_2N-phenyl; di(lower)alkyl-N-phenyl-; lower alkyl-O-phenyl-; and phenyl(lower)alkoxy-phenyl-, e.g., phenyl-CH_2-O-phenyl- (see page 1, line 31 of Tsutomu *et al.*). In the phenyl-CH_2-O-phenyl- group, "CH_2-O" corresponds to "X" of the present invention.

The following is what Applicants, in fact, argued in the Amendment and Reply filed on January 21, 2003. First, Applicants argued that Tsutomu *et al.* do not disclose any compounds where an optionally substituted phenyl-X-phenyl- is attached to the pyrimidine ring as follows:

> In none of the 1,2-dihydropyrimidine derivatives purportedly disclosed by Tsutomu *et al.* is the substituent R^1 an optionally substituted phenyl linked to an optionally substituted phenyl by one of –O-, -S-, -NH-, or $–CH_2$-.

(Amendment and Reply filed January 21, 2003, page 16, lines 10-12 from the bottom of the page).

As described above, in the phenyl-X-phenyl- group of Tsutomu *et al.*, X can only be "lower alkyl-O". Tsutomu *et al.* do not describe any compound having an optionally substituted phenyl-X-phenyl- group where X is O, S, NH, or CH_2.

Second, Applicants argued that Tsutomu *et al.* do not disclose any compounds where Applicants' R_1 is aminocarbonyl, i.e., $-C(O)NH_2$, when an optionally substituted alkyl-X-phenyl, i.e., R_7-X-phenyl-, is attached to the pyrimidine ring as required by the claims:

> Additionally, claims 1 and 63 of the present application require that when Y is R_7, i.e., when Applicants' X-Y is optionally substituted alkyl linked to the phenyl ring directly or by one of –O-, -S-, -NH-, or $–CH_2$-, Applicants' R_1 is aminocarbonyl. Tsutomu *et al.* do not disclose any compounds in which both (i) R^1 (which corresponds to Applicants' X-Y) is optionally substituted alkyl linked to the phenyl ring directly or by one of –O-, -S-, -NH-, or $–CH_2$-, and (ii) a substituent which corresponds to Applicants' R_1 is aminocarbonyl.

(Amendment and Reply filed January 21, 2003, page 16, lines 4-10 from the bottom of the page).

In fact, Tsutomu *et al.* purportedly describe a lower alkyl-O-phenyl- group as R^1 that corresponds to Applicants' R_7-X-phenyl- and fulfills the requirement (i) above. In this situation, however, Tsutomu *et al.* do not fulfill the second requirement (ii), i.e., the compound of Tsutomu *et al.* does not have a $–C(O)NH_2$ group attached to the pyrimidine moiety. As discussed above with regard to the rejection under 35 U.S.C. § 112, second

paragraph, the specification defines "aminocarbonyl" as "–$C(O)NH_2$". Therefore, contrary to the Examiner's allegations, the –C(O)NH-tetrazolyl group of Tsutomu *et al.* is not the same as Applicants aminocarbonyl, i.e., –$C(O)NH_2$. Thus, Tsutomu *et al.* do not describe any compound having both a lower alkyl-X-phenyl- group where X is O, S, NH, CH_2 or absent and a –$C(O)NH_2$ group attached to the pyrimidine moiety.

The Examiner refers to examples 11 and 15 of Tsutomu *et al.* on pages 10 and 11, respectively. Example 11 purportedly describes the following compounds: (1) 1,6-dihydro-6-oxo-2-(4-isopropoxyphenyl)pyrimidine-4-carbaldehyde dimethyl acetal; (2) 1,6-dihydro-6-oxo-2-(4-isopropoxyphenyl)pyrimidine-4-carbaldehyde; (3) 1,6-dihydro-6-oxo-2-(4-isopropoxyphenyl)pyrimidine-4-carboxylic acid; and (4) 1,6-dihydro-6-oxo-2-(4-isopropoxyphenyl)pyrimidine-4-[N-(5-tetrazolyl)]-carboxamide sodium salt.

First, none of the compounds of example 11 contain an optionally substituted phenyl-X-phenyl group attached to the pyrimidine moiety.

Second, all the compounds (1)-(4) of example 11 have a 4-isopropyl-O-phenyl- group attached to the pyrimidine moiety. The present claims require that in this situation, an aminocarbonyl group, i.e., Applicants' R_1 should be attached to the pyrimidine ring. As discussed above, according to the specification as originally filed, aminocarbonyl group is "-$C(O)NH_2$". See paragraph [0090] at page 19. None of the compounds (1)-(4) of example 11 include a -$C(O)NH_2$ group attached to the pyrimidine ring. The Examiner appears to include a COR_8 group where R_8 is a heterocyclic group in the definition of "aminocarbonyl." Applicants respectfully disagree and submit that there is no basis in the application as filed for any other definition for "aminocarbonyl" but "-$C(O)NH_2$" as defined at paragraph [0090].

In view of the above, none of the compounds (1)-(4) purportedly described in example 11 of Tsutomu *et al.* fall into the scope of the present claims.

Example 15 of Tsutomu *et al.* purportedly describe the following compounds: (1) 1,6-dihydro-6-oxo-2-(4-methoxyphenyl)pyrimidine-4-carbaldehyde dimethyl acetal; (2) 1,6-dihydro-6-oxo-2-(4-methoxyphenyl)pyrimidine-4-carbaldehyde; (3) 1,6-dihydro-6-oxo-2-(4-methoxyphenyl)pyrimidine-4-carboxylic acid; and (4) 1,6-dihydro-6-oxo-2-(4-methoxyphenyl)pyrimidine-4-[N-(5-tetrazolyl)]-carboxamide.

First, none of the compounds of example 15 contain an optionally substituted phenyl-X-phenyl group attached to the pyrimidine moiety.

Second, all the compounds (1)-(4) of example 15 have a 4-methyl-O-phenyl group attached to the pyrimidine moiety. As stated above, the present claims require that in this situation, an aminocarbonyl group, i.e., Applicants' R_1 should be attached to the pyrimidine ring. None of the compounds (1)-(4) of example 15 include a $-C(O)NH_2$ group attached to the pyrimidine ring.

In view of the above, none of the compounds (1)-(4) purportedly described in example 15 of Tsutomu *et al.* fall into the scope of the present claims.

Applicants have amended claims 1, 50, 63, 68, and 69 by replacing the term "aminocarbonyl" with -- —$C(O)NH_2$ -- in the proviso "provided that when Y is R_7, R_1 is aminocarbonyl" to make claims 1, 50, 63, 68, and 69 more clear. Support for this amendment is found at page 19, paragraph [0090], of the specification as originally filed.

It is respectfully submitted that Tsutomu *et al.* do not describe any compound or pharmaceutical composition that falls into the scope of independent claims 1, 50, 63, 68, 69, 72, or 73. Tsutomu *et al.* do not teach each and every element of claims 1, 50, 63, 68, 69, 72, or 73. Therefore, Tsutomu *et al.* do not anticipate claims 1, 50, 63, 68, 69, 72, or 73 or any claim dependent on these claims.

Furthermore, it is respectfully submitted that there is no motivation, with a reasonable expectation of success, in Tsutomu *et al.* for a person of ordinary skill in the art, to modify compounds of Tsutomu *et al.* in order to arrive at the compounds of the present invention.

Claim 61 is directed to a pharmaceutical composition comprising a compound as claimed in claim 59 or claim 60. It is respectfully submitted that the Examiner has found claims 59 and 60 allowable and, thus, the rejection of claim 61 was in error and should be withdrawn.

In view of the above, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) of claims 1, 50-51, and 61-69 are respectfully requested.

Objections and Allowable Subject Matter

The Examiner has objected to claims 39 and 59-60 as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Applicants respectfully traverse this objection. Applicants have amended claim 39 to be an

independent claim. Reconsideration and withdrawal of the objection to claims 39 and 59-60 are respectfully requested.

Applicants note with appreciation that the Examiner has found claims 39 and 59-60 allowable since specific species embraced in this claim are not taught or suggested by the art of record or from a search in the relevant art area.

It is respectfully pointed out that claim 61 recites compounds of allowable claims 59 or 60 and, thus, should also be found allowable.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn.

In view of the foregoing remarks, Applicants submit that the claimed invention, as amended, is neither anticipated nor rendered obvious in view of the prior art references cited against this application. Applicants therefore request the entry of the Amendment, The Examiner's reconsideration and reexamination of the application, and the timely allowance of the pending claims.

Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance.

Further, Applicants submit that the entry of the amendment would place the application in better form for appeal, should the Examiner dispute the patentability of the pending claims.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

John M. Covert
Attorney for Applicants
Registration No. 38,759

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1100 New York Avenue, N.W.
Suite 800
Washington, D.C. 20005-3934
(202) 371-2600

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